Spirometric changes in obstructive disease: after all, how much is significant?*,**

Alterações espirométricas em doenças obstrutivas: afinal, o quanto é relevante?

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Abstract

Objective: To establish the upper limits for changes in FEV_1, slow vital capacity (SVC), FVC, and inspiratory capacity (IC) after placebo administration in patients with airflow obstruction. **Methods:** One hundred and two adults with airflow obstruction (FEV_1 = 62 ± 19% of predicted) were included in the study. All of the participants performed SVC and FVC maneuvers before and after the administration of placebo spray. The changes in FEV_1, SVC, FVC, and IC were expressed as absolute values, percentage of change from baseline values, and percentage of predicted values, 95% CIs and 95th percentiles being calculated. Factor analysis was performed in order to determine how those changes clustered. **Results:** Considering the 95% CIs and 95th percentiles and after rounding the values, we found that the upper limits for a significant response were as follows: FEV_1 = 0.20 L, FVC = 0.20 L, SVC = 0.25 L, and IC = 0.30 L (expressed as absolute values); FEV_1 = 12%, FVC = 7%, SVC = 10%, and IC = 15% (expressed as percentage of change from baseline values); and FEV_1 = 7%, FVC = 6%, SVC = 7%, and IC = 12% (expressed as percentage of predicted values). **Conclusions:** In patients with airflow obstruction, IC varies more widely than do FVC and SVC. For IC, values greater than 0.30 L and 15% of change from the baseline value can be considered significant. For FVC, values greater than 0.20 L and 7% of change from the baseline value are significant. Alternatively, changes exceeding 0.20 L and 7% of the predicted value can be considered significant for FEV_1 and FVC. On factor analysis, spirometric parameters clustered into three dimensions, expressing changes in flows, volumes, and dynamic hyperinflation.

Keywords: Respiratory function tests; Spirometry; Bronchospirometry.

Resumo

Objetivo: Estabelecer os limites superiores para mudanças em VEF_1, capacidade vital lenta (CVL), CVF e capacidade inspiratória (CI) após o uso de placebo em pacientes com obstrução ao fluxo aéreo. **Métodos:** Cento e dois adultos com obstrução ao fluxo aéreo (VEF_1 = 62 ± 19% do previsto) foram incluídos neste estudo. Todos os participantes realizaram manobras de CVL e CVF antes e depois do uso de *spray* de placebo. As mudanças em VEF_1, CVL, CVF e CI foram expressas em valores absolutos, porcentagem de variação em relação aos valores basais e porcentagem dos valores previstos, e foram calculados os IC95% e os percentis 95. A análise fatorial foi realizada a fim de determinar como essas alterações se agrupavam. **Resultados:** Considerando os IC95% e percentis 95 e após o arredondamento dos valores, obtivemos os seguintes limites superiores para resposta significante: VEF_1 = 0,20 L, CVF = 0,20 L, CVL = 0,25 L e CI = 0,30 L (em valores absolutos); VEF_1 = 12%, CVF = 7%, CVL = 10% e CI = 15% (em porcentagem de variação em relação aos valores basais) e VEF_1 = 7%, CVF = 6%, CVL = 7% e CI = 12% (em porcentagem dos valores previstos). **Conclusões:** Em pacientes com obstrução ao fluxo aéreo, a CI apresenta maior variabilidade do que a CVF e a CVL. Para a CI, valores maiores que 0,30 L e 15% de variação em relação ao valor basal devem ser considerados significantes. Para CVF, valores maiores que 0,20L e 7% de variação em relação ao valor basal são significantes. Alternativamente, alterações de mais de 0,20 L e 7% do previsto no VEF_1 e na CVF devem ser consideradas significantes. Na análise fatorial, os parâmetros espirométricos se agruparam em três dimensões, expressando mudanças no fluxo, volume e hiperinsuflação dinâmica.

Descritores: Testes de função respiratória; Espirometria; Broncospirometria.

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Introduction

In patients with airflow obstruction, changes in spirometric values after bronchodilator use are indicative of reversibility if they exceed the natural variability. On the basis of two landmark studies,[1,2] first the American Thoracic Society (ATS)[3] and later the ATS/European Respiratory Society (ERS)[4] issued statements in which they recommended that an absolute change of 200 mL and a relative change of 12% from baseline values be used in order to classify bronchodilator response as significant. Those values have also been reported as being indicative of significant changes in FVC after bronchodilator use,[1,4] being widely used.

Changes occurring after bronchodilator use can also be expressed in terms of the percentage of predicted values.[5] In two studies,[6,7] FEV_1 values higher than 6.0% were recommended.[6,7] In one of those studies,[7] an FVC value of 6.0% was recommended.

The relief of dyspnea and the increase in exercise performance after bronchodilator use in patients with airflow obstruction are due to a reduction in lung hyperinflation, as evidenced by increased inspiratory capacity (IC), increased vital capacity, or both.[8-10] To our knowledge, a small, single-center study[6] is the only study in which the limits of variation in IC after placebo administration were evaluated.[6] Although studies have suggested a cut-off point for IC based on a relevant increase in exercise performance,[9,10] it remains to be shown whether such values exceed the normal variability.

Changes in spirometric parameters after bronchodilator use can express variations in flow, volume, or both. The objective of the present study was to establish the upper limits for changes in slow vital capacity (SVC) and FVC after placebo administration in a large sample of patients with airflow obstruction, as well as to determine how those parameters clustered on factor analysis.

Methods

The present study was conducted in a referral pulmonary function laboratory in the city of São Paulo, Brazil.

All of the patients who were found to have obstructive disease were asked to return to the laboratory for further spirometry after having discontinued the use of short- and long-acting β_2 agonists (for $\geq$ 12 h and for $\geq$ 24 h, respectively) and of short- and long-acting theophylline preparations (for $\geq$ 24 h and for $\geq$ 48 h, respectively). The patients were not required to discontinue the use of corticosteroids. The diagnosis of asthma or COPD was based on medical records made by specialists.

All of the study participants gave written informed consent, and the study protocol was approved by the local research ethics committee.

A total of 102 adults with airflow obstruction (asthma, COPD, or both) performed SVC maneuvers and, subsequently, FVC maneuvers. All patients had been stable in the last 30 days. Airflow obstruction was characterized by an FEV_1/FVC ratio below the 5th percentile of the predicted value.

The spirometric tests were performed with a SensorMedics spirometer (Vmax229d; SensorMedics, Yorba Linda, CA, USA), which was calibrated daily. All SVC and FVC measurements were performed in accordance with the ATS/ERS criteria,[11] SVC being assessed during an expiratory maneuver.

A minimum of three acceptable SVC measurements were obtained. The difference between the highest SVC value and the second highest SVC value was < 0.150 L. For SVC, the largest value obtained from at least three acceptable maneuvers was recorded. For IC, at least three acceptable maneuvers were performed. The difference between the largest IC value and the second largest IC value was < 0.100 L. For IC, the values derived from the largest SVC were reported. The reference values for forced spirometry and IC were those reported in studies conducted in Brazil.[12,13] Within 15 min after the administration of four sprays of placebo, all tests were repeated in the same order, and the same acceptability and reproducibility criteria were applied.

General data are expressed as mean ± SD. The spirometric changes occurring after placebo administration are expressed as follows: absolute (post-baseline) values; percentage of change from baseline values (post-baseline × 100/baseline); and percentage of predicted values (post-baseline × 100/predicted).

The distribution of absolute changes induced by placebo was tested for normality by the Kolmogorov-Smirnov test and the Shapiro-Wilk test, as well as by analysis of normality plots,

the skewness coefficient, the kurtosis coefficient, extreme values, and outliers being assessed.[14] Outliers were not excluded from the analysis. Although the variations in SVC and IC showed normal distribution, the variations in FEV_1 and FVC did not. The upper limits were calculated by 95th percentiles and 95% CIs.

The correlations of the different expressions of spirometric changes after placebo administration with anthropometric variables were determined by Spearman's test. A two-tailed t-test was used for between-group comparisons.

For factor analysis, a correlation matrix was constructed, and the principal components were derived. A correlation coefficient > 0.30 was considered significant. Factors with an eigenvalue > 1 on principal component analysis were included in varimax rotation. For the final model, a scree plot was employed for factor selection, and three factors were retained. The next step was to construct a new factor matrix in order to examine the weight assigned to each variable per factor.

All statistical analyses were performed with the IBM SPSS Statistics software package, version 17.0 (IBM Corporation, Armonk, NY, USA). Values of $p < 0.05$ were considered statistically significant.

Results

The clinical and spirometric data before the administration of placebo are shown in Table 1. Patient age ranged from 25 years to 80 years. Females predominated, as did patients with a diagnosis of asthma. In 17, 35, and 50 of the patients, respectively, FEV_1 was ≤ 40% of the predicted value, 40–59% of the predicted value, and ≥ 60% of the predicted value.

There were differences between asthma and COPD patients in terms of the baseline percentage of predicted FEV_1 (FEV_1%). In the 64 patients with asthma, FEV_1% was 65.3 ± 18.5, compared with 54.1 ± 19.8 in the 34 COPD patients ($t = 2.78$; $p = 0.006$). However, the absolute variation in FEV_1 after the administration of placebo was similar between the two groups of patients: −0.043 ± 0.122 mL in the patients with asthma and −0.009 ± 0.133 mL in those with COPD ($t = 1.29$; $p = 0.20$).

There were no differences between males and females in terms of the absolute changes in FEV_1 (−0.045 ± 0.147 mL vs. −0.043 ± 0.147 mL; $t = 1.50$; $p = 0.124$).

On one-sample analysis, there was no evidence of any learning effect, the mean changes after the administration of placebo being nonsignificantly different from zero.

Table 2 shows the means, 95% CIs, and 95th percentiles for SVC, IC, FVC, and FEV_1 after the administration of placebo, in terms of absolute values, percentage of change from baseline values, and percentage of predicted values. After rounding the values derived from these two methods, we obtained significant values for changes in the spirometric parameters under study (Table 3).

Spearman's test revealed no significant correlation between changes in the spirometric parameters and their initial values (data not shown). Similarly, there were no correlations between changes in the spirometric parameters and age or between changes in the spirometric parameters and height.

Significant correlations were found between changes in FEV_1 and changes in FVC ($r_s = 0.62$; $p < 0.001$), between changes in SVC and changes in FVC ($r_s = 0.40$; $p < 0.001$), and between changes in SCV and changes in IC ($r_s = 0.22$; $p = 0.017$). By factor analysis, three factors were selected from the scree plot, explaining 92.5% of the total variance of changes after the administration of placebo. The first factor included changes in FEV_1 and FVC, the second factor included

Table 1 - Clinical data and pulmonary function test results before the administration of placebo in 102 patients with airflow obstruction.

Variable	Result
Gender	
Male, n	39
Female, n	63
Age (years), mean ± SD	55 ± 11
Smoking status	
Nonsmoker, n	50
Former smoker, n	42
Current smoker, n	10
Diagnosis	
COPD, n	34
Asthma, n	64
COPD and asthma, n	4
FEV_1/FVC% (% of predicted) mean ± SD	56 ± 12
VC (% of predicted), mean ± SD	89 ± 17
FVC (% of predicted), mean ± SD	88 ± 17
FEV_1 (% of predicted), mean ± SD	62 ± 19
IC (% of predicted), mean ± SD	83 ± 18

IC: inspiratory capacity.

Table 2 - Mean variations, 95% CIs, and 95th percentiles for the absolute values, percentage of change from baseline values, and percentage of predicted values for spirometric parameters after placebo administration.

Parameter	Absolute			% of change from baseline			% of predicted		
	Mean	95% CI	95th percentile	Mean	95% CI	95th percentile	Mean	95% CI	95th percentile
SVC	−0.030	0.237	0.222	−0.890	9.5	7.5	−0.920	7.4	6.0
IC	−0.006	0.283	0.317	0.034	14.1	15.4	−0.114	11.2	12.5
FVC	−0.012	0.198	0.227	−0.283	7.3	6.5	−0.213	6.3	5.6
FEV_1	−0.020	0.192	0.159	−0.796	12.3	12.7	−0.549	7.3	7.4

SVC: slow vital capacity; and IC: inspiratory capacity.

Table 3 - Significant variations for absolute values, percentage of change from baseline values, and percentage of predicted values for spirometric parameters after placebo administration.

Variation	Absolute	% of change from baseline	% of predicted
SVC	0.25	10	7
IC	0.30	15	12
FVC	0.20	7	6
FEV_1	0.20	12	7

SVC: slow vital capacity; and IC: inspiratory capacity.

Table 4 - Rotated component matrix for variations in spirometric parameters after placebo administration.

Parameter	Component		
	1	2	3
FEV_1	0.935		
FVC	0.866	0.304	
SVC		0.976	
IC			0.994

SVC: slow vital capacity; and IC: inspiratory capacity.

changes in SVC and FVC, and the third factor included changes in IC only (Table 4).

Discussion

In the present study, we propose upper limits for random short-term variations in parameters assessed by SVC and FVC maneuvers in a sample of patients with airflow obstruction. The variations in FEV_1 were found to be the same as those found in previous studies. However, values for variations in FVC, when expressed as percentage of change from baseline values, were lower. This is the first study to derive values for changes in SVC and IC from a large sample.

Regarding the use of bronchodilators in a pulmonary function laboratory setting,[7] some questions remain:

- What are the most appropriate parameters to express bronchodilator response?
- What is the best way to express the changes occurring after medication use?
- What is the threshold that correlates with clinically significant outcomes?

Because it has the greatest sensitivity, the lowest variability, and the best reproducibility, FEV_1 is the most widely used spirometric parameter.[7] The ATS and the ERS proposed FEV_1 and FVC increases of at least 0.20 L and of 12% of change from baseline values[4] on the basis of two studies.[1,2] One of those studies evaluated the changes occurring after the administration of placebo in 40 patients.[1] The 95% CI for FEV_1 was 0.18 L when expressed in absolute values and 12.3% when expressed as percentage of change from baseline values. In the present study, these values were 0.19 L and 12.3%, respectively, and, when derived from the 95th percentile, 0.16 and 12.7%. In patients with low FEV_1 values, the change in FEV_1 after bronchodilator use commonly exceeds the limit of 12% of change from the baseline value. Therefore, it has been suggested that absolute and relative changes should be considered when evaluating the bronchodilator response. In the same study,[1] the upper limits for FVC were 0.34 L (absolute value) and 14.9% (percentage of change from the baseline value). In the present study, the FVC values derived from the 95% CI were 0.20 L and 7.3%, whereas those derived from the 95th percentile were 0.23 L and 6.5%. After rounding these values, we propose that the upper limits

be set at 0.20 L and 7%. The ATS and the ATS/ERS[3,4] have stated that the variations in FVC should be the same as those in FEV_1, probably on the basis of the expected short-term variability in FEV_1 and FVC in spirometric maneuvers. Although the upper limit for absolute changes in FVC found in the present study is similar to those suggested by the ATS, the values for the percentage of change from baseline values are much lower. This will increase the sensitivity of FVC for detecting changes in lung function in a pulmonary function laboratory setting. In another study,[2] 150 patients with obstructive disease underwent two spirometric tests, 20 minutes apart. The increases in FEV_1 and FVC required in order to exclude a random variation by 95% CI were 0.16 L and 0.33 L, respectively. In a more recent study, FEV_1 and FVC variations were evaluated after the administration of placebo in 98 patients with COPD.[7] The upper limit was found to be 0.18 L for FEV_1 and 0.28 L for FVC.

The most common ways of expressing the bronchodilator response are absolute changes, percentage of change from baseline values, and percentage of predicted values. Measurements based on predicted values have the best reproducibility and are the least dependent on baseline values.[5] The values derived in the present study suggest that increases ≥ 7% in the predicted FVC and FEV_1 values exceed the natural variability and can therefore be considered significant. For the sake of the reproducibility of the maneuvers, we believe that changes ≥ 0.20 L should also be present in order to characterize a significant response to bronchodilator use.

The bronchodilator response evaluated by FEV_1 has few, if any, clinical implications for COPD. The bronchodilator response varies according to the setting.[15] The lack of response in a laboratory setting does not translate to a lack of clinical response to bronchodilators or inhaled corticosteroids, as evaluated by short-term relief of dyspnea, long-term relief of dyspnea, improved quality of life, improved exercise capacity, and changes in FEV_1.[9,10,16,17]

Two types of studies have been used in order to derive cut-off points intended to characterize a significant bronchodilator response. Post-bronchodilator variations can be considered significant if they exceed those observed in individuals without lung disease or if they exceed the spontaneous variation observed after the administration of placebo in patients with airflow limitation, such as those investigated in the present study. In individuals without lung disease, FEV_1 increases by less than 10% after bronchodilator use.[1,18,19] This cut-off point has been used for distinguishing between asthma and COPD patients in some studies.[20,21] However, this limit can be exceeded in some patients with COPD, especially if a combination of beta-agonists and anticholinergic agents is used.[22]

Hyperinflation is a physiological change that is characteristic of many patients with COPD. Airway obstruction leads to progressive air trapping during exhalation, as well as leading to hyperinflation. These changes result in reduced resting IC, increased work of breathing, and lower exercise tolerance.[8,9] Dynamic hyperinflation has been shown to be an independent predictor of decreased daily physical activity and mortality due to respiratory failure in patients with COPD.[23]

Bronchodilators reduce hyperinflation at rest and during exercise.[8-10] It is possible that patients with COPD who do not show a significant response to bronchodilators as assessed by flow (FEV_1) will show a significant lung volume response as assessed by increased SVC and IC.[24] Increased IC has been associated with decreased hyperinflation and improved exercise tolerance.[8-10] Many studies involving different classes of bronchodilators have shown associations among increased IC, improved exercise tolerance, and reduced dyspnea in COPD patients.[25] However, changes in IC after placebo administration are poorly characterized. In a study involving 26 patients with asthma or COPD, the proposed limit for IC changes after placebo administration was a 9% increase from baseline values or 220 mL.[6] In two studies, an increase of more than 0.3 L in IC was associated with a significant improvement in exercise tolerance in patients with COPD.[9,10] In the present study, IC increases of more than 15% in relation to the baseline values, of more than 12% in the predicted values, and of 0.3 L were found to constitute the upper limit for IC after the administration of placebo, values that are similar to those found in those studies.[9,10] For SVC, increases of more than 0.25 L, of more than 10% in relation to baseline values, or of more than 7% in the predicted values can be considered significant.

Bronchodilator responses can be categorized as flow responses or volume responses. When post-

bronchodilator changes in FEV_1 are proportional to the post-bronchodilator changes in FVC, they can reflect lung volume recruitment and should be considered volume responses.[26] Although FEV_1 and FVC are volume measurements, post-bronchodilator variations in these measurements can reflect increased expiratory flow. An isolated post-bronchodilator variation in FEV_1 probably reflects bronchial dilation primarily of the central airways, whereas an isolated post-bronchodilator variation in FVC is indicative of bronchial dilation primarily of the peripheral airways. Patients with more severe airflow obstruction commonly show an isolated FVC response,[27] which reflects the emptying of very slow lung compartments. Therefore, FEV_1 and FVC both also reflect changes in flow, albeit in different segments of the tracheobronchial tree. It is therefore not surprising that we found a correlation between FEV_1 changes and FVC changes in the present study, those changes having shared a common factor (factor 1) on factor analysis. In addition, FVC correlated and clustered with SVC on factor analysis (factor 2). A volume response is characterized by an increase in SVC and in FVC.

Interestingly, our factor analysis showed no association between variations in IC and variations in SVC, although a significant but weak correlation was found between those two variables. In patients with lung hyperinflation, a reduction in RV is expected after the use of a bronchodilator, reflected by an increase in SVC.[28,29] However, studies including unselected patients have found a poor but significant correlation between variations in RV and variations in SVC.[30] It is known that TLC can decrease after bronchodilator use, and this interferes with the abovementioned correlation.[28] The changes in SVC after bronchodilator use are inferior to the variation in IC in predicting exercise capacity improvement in COPD patients.[9,10] The real operational limit for volume expansion in air flow during exercise is IC rather than SVC. Although FVC also increases with the reduction in RV after bronchodilator use, FVC is inferior to SVC because it is influenced by thoracic gas compression during forced expiration (as is FEV_1). This finding is made even more evident with accentuated hyperinflation.[24]

One of the possible limitations of the present study is the inclusion of a large proportion of female asthma patients with mild airflow obstruction. However, there were no differences between the patients with asthma and those with COPD in terms of the variations in the parameters studied, and there were no correlations between FEV_1% and the variation in FEV_1 after the administration of placebo.

In conclusion, we established cut-off points for changes in parameters derived from SVC and FVC maneuvers performed after the administration of placebo in a large sample of patients with airflow obstruction. On factor analysis, these parameters clustered into three dimensions, expressing changes in flows, volumes, and dynamic hyperinflation.

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